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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Jon A. Weidanz

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EXAMINER

SCHWADRON, RONALD B

ART UNIT

PAPER NUMBER

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DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 09/874,907	Applicant(s) WEIDANZ ET AL.	
	Examiner Ron Schwadron, Ph.D.	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 81,82,84-100,102-125 and 147-156 is/are pending in the application.
- 4a) Of the above claim(s) 84,87-100,103-123,125 and 154-156 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 81,82,85,86,102,124 and 147-153 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

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1. Applicant's election with traverse of the species elected in the reply filed on 1/7/10 is acknowledged. The traversal is on the ground(s) that are stated. This is not found persuasive because the species are distinct for the reasons elaborated in the previous Office Action. In addition, applicant has indicated that the aforementioned species are distinct.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 154-156 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/14/09.

3. Claims 81,82,85,86,102,124,144-153 are under consideration.

4. The amendment filed 9/14/09 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows. The added material which applicant is attempting to incorporate by reference.

The attempt to incorporate subject matter into this application by reference is ineffective because there was no specific reference in the specification to the *specific constructs* that applicant is attempting to add to the specification.

Applicant is required to cancel the new matter in the reply to this Office Action.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 81,82,85,86,102,124,144-153 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants arguments have been considered and deemed not persuasive.

a) There is no support in the specification as originally filed for the recitation of “alpha and beta variable chain covalently linked together by a second peptide linker” in claim 81.

The specification as originally filed does not disclose constructs containing only a Valpha and a Vbeta and also does not disclose such constructs linked by a peptide linker. The specification as originally filed discloses a variable alpha chain linked to a variable beta and Cbeta, but does not disclose a construct that lacks the Cbeta. The claims under consideration encompass TCR constructs without a Cbeta and such constructs are not disclosed in the specification as originally filed. Regarding applicants comments, the actual cited example to which applicant refers contains a Cbeta. The claims under consideration encompass TCR constructs without a Cbeta and such constructs are not disclosed in the specification as originally filed. Regarding applicants comments about page 20 of the specification, said passage does not refer to constructs containing only a Valpha and a Vbeta and also does not disclose such constructs linked by a peptide linker. Regarding the subject matter which applicant has attempted to incorporate by reference, said material constitutes new matter for the reasons stated above.

b)-d) The previous pending rejections of claims 144-146 as per sections b)-d) of this rejection as recited in the previous Office action is withdrawn in view of the cancellation of said claims.

e) There is no support in the specification as originally filed for the limitation of claim 147/148/149/151/152. The previously cited passage of the specification discloses said linkers between a TCR and a biologically active molecule, but does not disclose said linkers as used between an alpha and beta chain of a TCR.

Regarding applicants comments, the specification discloses said linkers between a TCR and a biologically active molecule, but does not disclose said linkers as used

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between an alpha and beta chain of a TCR. None of the examples cited by applicant disclose a linker consisting of ALA, SER and GLY connecting an alpha and beta TCR chains wherein said linker includes from about 8 to 16 amino acids. None of the examples cited by applicant disclose a construct with two linkers wherein the first and second linker encompass any peptides of about 7 to 20 amino acid. . None of the examples cited by applicant disclose a construct with two linkers wherein the first and second linker encompass any peptides of about 8 to 16 amino acid.

There is no support in the specification as originally for the scope of the claimed inventions (aka the claimed inventions constitute new matter).

Regarding applicants comments about the specification, page 20, said passage does not disclose the linkers recited in the claims as used between an alpha and beta chain of a TCR. Regarding applicants comments about the specification, pages 30 and 31, said examples refer to use of a specific linker of a specific length in a construct that also contains a C beta chain wherein the claims under consideration are not limited to such constructs.

f) There is no support in the specification as originally filed for the invention of claim, 153. The specification as originally filed does not disclose constructs containing only a Valpha and a Vbeta and also does not disclose such constructs linked by a peptide linker. The specification as originally filed discloses a variable alpha chain linked to a variable beta and Cbeta, but does not disclose a construct that lacks the Cbeta. The claims under consideration encompass TCR constructs without a Cbeta and such constructs are not disclosed in the specification as originally filed. Regarding the subject matter which applicant has attempted to incorporate by reference, said material constitutes new matter for the reasons stated above.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 81,82,85,86,102,124,147-153 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weidanz et al. (WO 99/18129) in view of Bonneville et al. (US Patent 5,723,309). Applicants arguments have been considered and deemed not persuasive.

Weidanz et al. teach a soluble single chain alpha beta TCR wherein the Valpha and Vbeta chain are connected by a linker(see claims 1,2,4 and page 4, penultimate paragraph). The alpha beta chains of the TCR are covalently linked by the linker of claim 147 ((see page 24, last paragraph) wherein the optimal length would be determined via routine experimentation. The linker can contain the amino acids of claim 149 (see page 24, last paragraph). The TCR can be specific for a single antigen such as P53 wherein the TCR recognizes said antigen in the context of HLA A2.1 (see page 34, first paragraph). Weidanz et al. teach said TCR in a pharmaceutical (aka therapeutic) composition (see page 42). Weidanz et al. teach said TCR in a fusion protein containing an effector molecule wherein said effector is attached to the Valpha /Vbeta chain via an intervening C κ or C λ chain wherein said chain would function as a "peptide linker" (see claim 43). The "includes" of claim 148 is interpreted as equivalent in scope to "comprising". Weidanz et al. do not teach that the effector molecule is a cytokine. Bonneville et al. teach soluble TCR fusion proteins wherein a TCR is linked to IL-2 (see column 3, lines 40-52 and column 2, last four paragraphs). Bonneville et al. teach a therapeutic composition containing soluble TCR fusion proteins wherein a TCR is linked to IL-2 (see column 5, lines 52-56). Bonneville et al. teach that the TCR can be a covalently linked single chain TCR containing alpha and beta chain variable regions (see abstract and column 2, penultimate paragraph). IL-2 is specific for recognition of an

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effector cells (immune cells expressing IL-2 receptor such as activated T cells). Bonneville et al. disclose that said TCR/IL-2 fusion proteins can be used to treat disease (see column 5, lines 57-60). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Weidanz et al. teach the claimed TCR fusion proteins except for use of IL-2 whilst Bonneville et al. teach soluble TCR fusion proteins wherein a TCR is linked to IL-2. One of ordinary skill in the art would have been motivated to do the aforementioned because Weidanz et al. teach said TCR in a fusion protein containing an effector molecule whilst Bonneville et al. teach soluble TCR fusion proteins wherein a TCR is linked to IL-2 and that said TCR/IL-2 fusion proteins can be used to treat disease.

Regarding applicants comments about unpredictability of folding of cytokines, Bonneville et al. teach a therapeutic composition containing soluble TCR fusion proteins wherein a TCR is linked to IL-2 (see column 5, lines 52-56). Bonneville et al. teach that the TCR can be a covalently linked single chain TCR containing alpha and beta chain variable regions (see abstract and column 2, penultimate paragraph). The prior art is enabled in the absence of evidence to the contrary and no such evidence has been provided by applicant. Regarding applicants comments about linker size, the only claim that actually specifies the length of the effector molecule/TCR linker molecule is claim 148/149/151/152. The "includes" of claim 148 is interpreted as equivalent in scope to "comprising" wherein the linker could therefore encompass additional amino acids. The size of the linker would have been determined by routine experimentation. Regarding applicants comments about Bonneville et al., Weidanz et al. teach a soluble single chain alpha beta TCR wherein the Valpha and Vbeta chain are connected by a linker(see claims 1,2,4 and page 4, penultimate paragraph). The alpha beta chains of the TCR are covalently linked by the linker of claim 147 ((see page 24, last paragraph) wherein the optimal length would be determined via routine experimentation. The linker can contain the amino acids of claim 149 (see page 24, last paragraph). Bonneville et al. teach a therapeutic composition containing soluble TCR fusion proteins wherein a TCR is linked to IL-2 (see column 5, lines 52-56). Bonneville et al. teach that the TCR can be a covalently linked single chain TCR containing alpha and beta chain variable regions (see abstract and column 2, penultimate paragraph). The prior art is enabled in the

absence of evidence to the contrary and no such evidence has been provided by applicant. Regarding applicants reference to Ju et al., said publication is not of record and a copy has not been furnished so applicants comments regarding said reference have not been considered. Regarding applicants comments about the N-terminus of IL-2, Bonneville et al. teach that the IL-2 **molecule contains the entire IL-2 molecule (aka it contains the N-terminus)**. The attachment of the molecule to the N-terminus of IL-2 versus the presence of the intact molecule are two unrelated issues.

Furthermore, regarding applicants various assertions about the enablement of the prior art, the MPEP section 716.01(c) [R-2] states:

>II. < ATTORNEY ARGUMENTS CANNOT TAKE THE PLACE OF EVIDENCE

*The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, **inoperability of the prior art**, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.*

Regarding the Wong declaration, there is no disclosure in said declaration of the actual structure of the constructs used or how they were made. Thus, it is unclear as to whether said constructs are encompassed by the claims under consideration and it is unclear if said constructs were made using methods disclosed in the specification. Thus, the relevance of the Wong declaration to the claimed invention is unclear. Regarding applicants comments and the Wong declaration, **there is no disclosure in said declaration of the actual structure of the constructs used or how they were made. Thus, it is unclear as to whether said constructs are encompassed by the claims under consideration and it is unclear if said constructs were made using methods disclosed in the specification.** Regarding applicants assertions as to what constructs Wong was referring to, the MPEP section 2145, section I. discloses:

The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d

1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Regarding applicants comments about the “claimed fusion molecule”, in view of the fact that Declarant Wong is not a trained practitioner of patent law, it is unclear as to what this phrase means as used by Wong or what Wong envisions this phrase as meaning. Regarding applicants comments about methods of making the claimed molecules, if the method of making the product is not disclosed in the specification and the method renders the product different than disclosed in the specification than that information would be germane to the results disclosed in the declaration. In addition, the Wong declaration does not compare the claimed invention to the closest prior art (aka the fusion proteins taught by Bonneville et al.).

8. The rejection of claim 146 under 35 U.S.C. 103(a) as being unpatentable over Weidanz et al. (WO 99/18129) in view of Bonneville et al. (US Patent 5,723,309) as applied to claims 81,82,85,86,102,124,144,145,147-150 above, and further in view of Theobald et al. for the reasons elaborated in the previous Office Action is withdrawn in view of the cancellation of said claim

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron, Ph.D. whose telephone number is 571 272-0851. The examiner can normally be reached on Monday-Thursday 7:30-6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ron Schwadron/

Ron Schwadron, Ph.D.

Primary Examiner, Art Unit 1644